REMARKS

The courtesy of Examiner Shahnan-Shah and Examiner Schwartz in extending Applicants' representative a telephone interview on September 9, 2003, is noted with appreciation. During that interview, the remaining rejection of claims under 35 U.S.C. § 103 was discussed the Examiners. Examiner Shahnan-Shah requested that Applicants file a written response to her Advisory Action dated July 26, 2003, and indicated that such a response would be considered.

This paper is the written response to the Advisory Action requested by the Examiner. Allowance of all of the currently pending claims (Claims 48-68) is respectfully requested in view of the remarks below.

A. Restriction Requirement

As noted in Applicants' previous response, Claim 55 reads on the elected species, cobalt. It should not, therefore, have been withdrawn from consideration.

B. Rejection Under 35 U.S.C. § 103

Claims 48, 49, 50-53, 56-58, 60-61, 63-64 and 66-68 continue to be rejected as being unpatentable over U.S. Patent No. 5,227,307 (Bar-Or et al.) in view of U.S. Patent No. 5,994,339 (Crapo et al.) and U.S. Patent No. 6,375,930 (Young et al.). Applicants respectfully traverse this rejection for the reasons already of record and for the following additional reasons.

Contrary to the Examiner's contentions, the combined teachings of the prior art do not teach or suggest the claimed invention. Indeed, the Examiner has failed to demonstrate even a *prima facie* case that the claimed invention would have been obvious at the time it was made and has improperly reconstructed the invention through hindsight. In particular, as will be shown in the discussion below, the Examiner has failed to show any suggestion or motivation in the prior art for combining the teachings of the cited references. Instead, it is submitted that the Examiner's source of the motivation to combine the references is the present application, and the combination of references in a manner that reconstructs the invention only with the benefit of hindsight is insufficient to present a *prima facie* case of obviousness.

The claims of the present application are directed to a method of monitoring or assessing treatment of a patient suffering from a disease or condition. The patient is treated with a drug that

produces free radicals or a drug that reduces free radicals. The claims do not cover assessing or monitoring treatment of a patient with other drugs or other treatments of a patient, such as angioplasty.

In the Advisory Action, the Examiner states:

> It is the examiner's position that Bar-Or et al. teach or suggest monitoring or assessing the effectiveness of treatment of patients for example in column 2, lines 23-25 Bar-Or et al. recite "A further object of the invention is to provide a method for evaluating rehabilitated patients suffering from ischemia (myocardial infraction [sic, infarction]) to determine circulatory effectiveness", in column 9 lines 34-41 Bar Or et al. recite "The results indicate that the present method can be used to detect ischemic states. The present method is effective in distinguishing between ischemic cardiogenic chest pain and non-cardiogenic chest pain. Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced other than as specifically described herein.

As noted above, the present claims are not directed to monitoring or assessing the effectiveness of any and all treatments. Instead, the claims are directed to monitoring and assessing the effectiveness of two specific treatments - treatment with drugs that produce free radicals or treatment with drugs that reduce free radicals. The language of Bar-Or et al. relied on by the Examiner does not teach or suggest monitoring or assessing the effectiveness of the specific treatments covered by Applicants' claims.

In particular, Bar-Or et al. is directed to the diagnosis of one specific condition - ischemia (see, *e.g.*, column 1, lines 7-11, column 2, lines 20-45, of Bar-Or et al.). The express language of lines 23-25 of column 2 of Bar-Or et al. relied on by the Examiner makes it clear that the rehabilitation referred to would be as a result of rehabilitative treatments for ischemia, such as angioplasty or rest and is performed to determine circulatory effectiveness. It is submitted that this statement cannot reasonably to be interpreted to mean any other kind of treatment of patients. In particular, this statement does not teach or suggest the specific treatments of patients with drugs that produce or reduce free radicals covered by the present claims.

The first two sentences of lines 34-41 of column 9 simply reiterate that the Bar-Or et al. method is effective in detecting ischemia. The remainder of the quoted language is standard "boilerplate" language used in numerous patents. In the context of the Bar-Or et al. patent, the "modifications and variations" of the invention and the practice of the invention "within the scope

of the appended claims" would still be for the detection of ischemia, since Bar-Or et al. is directed only to the diagnosis of this one specific condition (see, *e.g.*, column 2, lines 20-45, and Claims 1-13 of Bar-Or et al.). In any event, this very general language in no way teaches or suggests monitoring or assessing the effectiveness of the treatment of patients with drugs that produce or reduce free radicals.

This very general language also does not provide any motivation for those skilled in the art to *combine* the teachings of Bar-Or et al. with those of Crapo et al. and Young et al., contrary to the Examiner's contention in the first full paragraph on page 4 of the Advisory Action.

Indeed, Applicants submit that there is no basis in the prior art for combining the teachings of Bar-Or et al. with those of Crapo et al. and Young et al., and that the Examiner has improperly reconstructed the invention through hindsight. Applicants submit that the only possible reason for choosing the Crapo et al. and Young et al. references and combining them with Bar-Or et al. is as a result of knowledge the Examiner obtained by reviewing Applicants' disclosure. As noted in the previous paragraph, the very general statements at lines 34-41 of column 9 of Bar-Or et al. are inadequate to provide motivation for those skilled in the art to combine the teachings of Bar-Or et al. with those of Crapo et al. and Young et al. Moreover, there is nothing in Crapo et al. or Young et al. that lead one to combine these references with Bar-Or et al. to arrive at the invention and the Examiner has not pointed to anything in these references to support a motivation to combine.

The CAFC has made it extremely clear that hindsight reconstruction is always improper. See, *e.g.*, *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). In particular, the prior art must be only that which a person skilled in the art would have selected without the advantage of hindsight or knowledge of the claimed invention. *Union Carbide Corp. v. American Can Co.*, 724 F.2d 1567, 220 USPQ 584 (Fed. Cir. 1984).

Finally, even assuming that the Examiner's interpretation of the very general statements found at lines 34-41 of column 9 of Bar-or et al. is correct, an interpretation which Applicants strongly contend is erroneous, these very general statements would not have led a person skilled in the art to select the Crapo et al. reference, the Young et al. reference or any other specific reference(s). At best, other than with respect to the field of detection of ischemia, these statements are an invitation to experiment to find additional uses for the Bar-Or et al. method. Applicants submit that these

statements do not even rise to this level, but an invitation to experiment is, of course, not the standard of obviousness. *See, e.g., In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

In the Advisory Action, the Examiner also states:

> It is also the examiner's position that [the] claims are drawn to a method of monitoring or assessing treatment of a disease or condition that produces free radicals. . . . The instant specification in the paragraph bridging pages 12 and 13 recites, "The methods of the invention can be used to monitor and assess disease and conditions in which free radicals play a role." The paragraph further recites ischemia as one of these conditions (see page 13, line 4). Therefore, the invention is obvious over Bar-Or et al. In view of Crapo et al. and further in view of Young et al.

The Examiner is incorrect about the coverage of the present claims. As noted above, Applicants' claims are not directed to monitoring or assessing *disease and conditions in which free radicals play a role* or *any and all treatments for a disease*. They are drawn to monitoring or assessing two specific treatments - treatments with drugs that produce or reduce free radicals.

Applicants note the Examiner's reliance on certain statements contained in Applicants' specification. However, the present application describes and claims more than one invention, and the statements relied on by the Examiner do not describe the *claimed invention* that the Examiner is currently examining. Compare the portion of the specification cited by the Examiner with the first full paragraph on page 13 and the paragraph bridging pages 14-15. Also, compare the currently pending claims with Claims 76-99.

Moreover, the Examiner's reliance on Applicants' specification underscores the improper hindsight nature of the Examiner's analysis. Indeed, the Examiner actually uses the teachings of Applicants' specification to expressly justify the combination of the three cited references. It is hard to imagine a clearer case of hindsight reconstruction.

Finally, during the interview, the Examiner expressed the opinion that Bar-Or et al. teaches all of the steps of the method for quantitating free radical damage. However, this is not correct.

Bar-Or et al. describes a method of detecting ischemia by contacting a patient sample with a metal ion that is capable of binding to proteins in the sample which contain thiol groups (see, *e.g.*, column 1, lines 9-11, and column 4, lines 49-54). Unbound metal ions are measured, and an increased amount of unbound metal ions is diagnostic of an ischemic event. Claims 48-59 of the

present application are directed to measuring bound metal ions. Nothing in Bar-Or et al. teaches or suggests measuring bound metal ions.

Bar-Or et al. hypothesizes that the number of thiol groups on the proteins in the patient sample is reduced by free radicals produced as a result of an ischemic event (see, *e.g.*, column 2, line 57, through column 3, line 11, of Bar-Or et al.). Bar-Or et al. further hypothesizes that the reduction in the number of thiol groups results in a reduction in the amount of metal ions bound by the proteins in a given sample, explaining why an increased amount of unbound metal ions provides a means of detecting an ischemic event. While Bar-Or et al. mentions other possible binding sites for metal ions on proteins besides the thiol groups (see column 3, lines 14-26, of Bar-Or et al.), only the thiol groups are believed to be altered as a result of the production of free radicals during ischemic events (see column 2, line 57, through column 3, line 11, of Bar-Or et al.). In particular, Bar-Or et al. does not teach or suggest that the N-terminus of albumin binds metal ions, that the metal-binding capacity of the N-terminus of albumin would be altered by free radicals, or that the N-terminus of albumin would be a relevant site for assessing free radical damage. It is the binding of metal ions to the N-terminus of albumin that is exploited in the present invention (see, *e.g.*, Claims 48-68).

For all of the foregoing reasons, the cited references would not have made the present invention obvious. Consequently, it is respectfully requested that the Examiner withdraw this rejection.

CONCLUSIONS

It is submitted that the pending claims are in condition for allowance, and a speedy allowance of them is requested.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: Angela Sebor

Angela Dallas Sebor
Registration No. 42,460
1560 Broadway, Suite 1200
Denver, CO 80202-5141
(303) 863-9700

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